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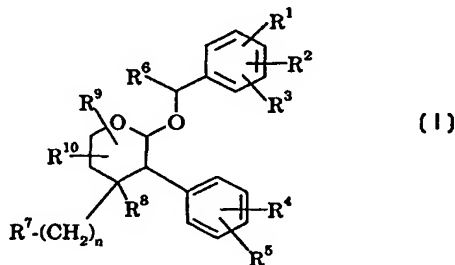
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(54) Title: TETRAHYDROPYRAN DERIVATIVES AND THEIR USE AS THERAPEUTIC AGENTS



(57) Abstract

The present invention relates to compounds of formula (I) wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^9$  and  $R^{10}$  represent a variety of substituents;  $R^6$  represents hydrogen or a  $C_{1-4}$ alkyl group optionally substituted by a hydroxy group;  $R^7$  represents halogen, hydroxy,  $C_{2-4}$ alkenyl,  $N_3$ ,  $-NR^{11}R^{12}$ ,  $-NR^aCOR^b$ ,  $-OSO_2R^a$ ,  $-(CH_2)_pNR^a(CH_2)_qCOOR^b$ ,  $COR^a$ ,  $COOR^a$ , or a five membered or six membered nitrogen-containing heteroaromatic ring optionally containing 1, 2 or 3 additional heteroatoms selected from N, O and S which heteroaromatic ring is optionally substituted at any substitutable position by a substituent selected from  $=O$ ,  $=S$ , halogen, hydroxy,  $-SH$ ,  $COR^a$ ,  $CO_2R^a$ ,  $-ZNR^{11}R^{12}$ ,  $C_{1-4}$ alkyl, hydroxy $C_{1-4}$ alkyl, fluoro $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, fluoro $C_{1-4}$ alkoxy or  $C_{1-4}$ alkoxy substituted by a  $C_{1-4}$ alkoxy or hydroxyl group;  $R^8$  represents hydrogen,  $C_{1-6}$ alkyl, fluoro $C_{1-6}$ alkyl, hydroxy,  $C_{1-6}$ alkoxy or hydroxy $C_{1-6}$ alkyl; and  $n$  is zero, 1 or 2; or a pharmaceutically acceptable salt thereof. The compounds are of particular use in the treatment or prevention of depression, anxiety, pain, inflammation, migraine, emesis or postherpetic neuralgia.

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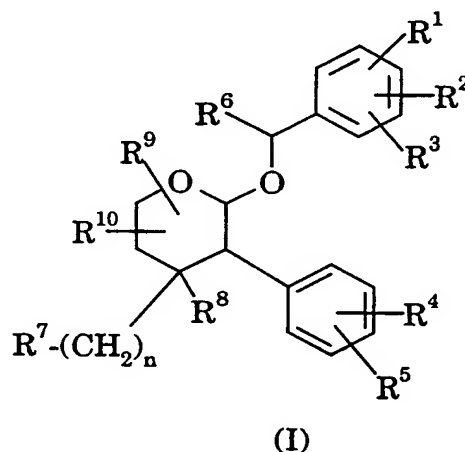
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**TETRAHYDROPYRAN DERIVATIVES AND THEIR USE**  
**AS THERAPEUTIC AGENTS**

This invention relates to a class of tetrahydropyran compounds which are  
5 useful as tachykinin antagonists. More particularly, the compounds of the  
invention are useful as neurokinin 1(NK-1) receptor antagonists.

The present invention provides compounds of the formula (I):



10

wherein

R<sup>1</sup> is hydrogen, halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, fluoroC<sub>1-6</sub>alkyl,  
fluoroC<sub>1-6</sub>alkoxy, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub>alkyl, NO<sub>2</sub>, CN, SR<sup>a</sup>, SOR<sup>a</sup>,  
SO<sub>2</sub>R<sup>a</sup>, CO<sub>2</sub>R<sup>a</sup>, CONR<sup>a</sup>R<sup>b</sup>, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl or C<sub>1-4</sub>alkyl substituted by  
15 C<sub>1-4</sub>alkoxy, wherein R<sup>a</sup> and R<sup>b</sup> each independently represent hydrogen or  
C<sub>1-4</sub>alkyl;

R<sup>2</sup> is hydrogen, halogen, C<sub>1-6</sub>alkyl, fluoroC<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy substituted  
by C<sub>1-4</sub>alkoxy;

R<sup>3</sup> is hydrogen, halogen or fluoroC<sub>1-6</sub>alkyl;

20

R<sup>4</sup> is hydrogen, halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, fluoroC<sub>1-6</sub>alkyl,  
fluoroC<sub>1-6</sub>alkoxy, hydroxy, NO<sub>2</sub>, CN, SR<sup>a</sup>, SOR<sup>a</sup>, SO<sub>2</sub>R<sup>a</sup>, CO<sub>2</sub>R<sup>a</sup>, CONR<sup>a</sup>R<sup>b</sup>,  
C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl or C<sub>1-4</sub>alkyl substituted by C<sub>1-4</sub>alkoxy, wherein R<sup>a</sup> and R<sup>b</sup>  
are as previously defined;

R<sup>5</sup> is hydrogen, halogen, C<sub>1-6</sub>alkyl, fluoroC<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy substituted  
25 by C<sub>1-4</sub>alkoxy;

R<sup>6</sup> represents hydrogen or a C<sub>1-4</sub>alkyl group optionally substituted by a hydroxy group;

R<sup>7</sup> represents halogen, hydroxy, C<sub>2-4</sub>alkenyl, N<sub>3</sub>, -NR<sup>11</sup>R<sup>12</sup>, -NR<sup>a</sup>COR<sup>b</sup>, -OSO<sub>2</sub>R<sup>a</sup>, -(CH<sub>2</sub>)<sub>p</sub>NR<sup>a</sup>(CH<sub>2</sub>)<sub>q</sub>COOR<sup>b</sup>, COR<sup>a</sup>, COOR<sup>a</sup>, or a five membered or six membered nitrogen-containing heteroaromatic ring optionally containing 1, 2 or 3 additional heteroatoms selected from N, O and S which heteroaromatic ring is optionally substituted at any substitutable position by a substituent selected from =O, =S, halogen, hydroxy, -SH, COR<sup>a</sup>, CO<sub>2</sub>R<sup>a</sup>, -ZNR<sup>11</sup>R<sup>12</sup>, C<sub>1-4</sub>alkyl, hydroxyC<sub>1-4</sub>alkyl, fluoroC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, fluoroC<sub>1-4</sub>alkoxy or C<sub>1-4</sub>alkoxy substituted by a C<sub>1-4</sub>alkoxy or hydroxyl group;

R<sup>8</sup> represents hydrogen, C<sub>1-6</sub>alkyl, fluoroC<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkoxy or hydroxyC<sub>1-6</sub>alkyl;

R<sup>9</sup> and R<sup>10</sup> each independently represent hydrogen, halogen, C<sub>1-6</sub>alkyl, CH<sub>2</sub>OR<sup>c</sup>, oxo, CO<sub>2</sub>R<sup>a</sup> or CONR<sup>a</sup>R<sup>b</sup> where R<sup>a</sup> and R<sup>b</sup> are as previously defined and R<sup>c</sup> represents hydrogen, C<sub>1-6</sub>alkyl or phenyl;

R<sup>11</sup> is hydrogen, C<sub>1-4</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkyl substituted by a C<sub>1-4</sub>alkoxy or hydroxyl group, or R<sup>11</sup> is a five membered or six membered nitrogen-containing heteroaromatic ring as previously defined;

R<sup>12</sup> is hydrogen or C<sub>1-4</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub>alkyl, or C<sub>2-4</sub>alkyl substituted by a C<sub>1-4</sub>alkoxy or hydroxyl group;

or R<sup>11</sup>, R<sup>12</sup> and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy, COR<sup>e</sup>, CO<sub>2</sub>R<sup>e</sup>, C<sub>1-4</sub>alkyl optionally substituted by a C<sub>1-4</sub>alkoxy or hydroxyl group, or C<sub>1-4</sub>alkoxy optionally substituted by a C<sub>1-4</sub>alkoxy or hydroxyl group, or a five membered or six membered nitrogen-containing heteroaromatic ring as previously defined, or said heteroaliphatic ring is substituted by a spiro-fused lactone ring, and said heteroaliphatic ring optionally containing a double bond, which heteroaliphatic ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or S(O)<sub>2</sub> or a second nitrogen atom which will be part of a NH or NR<sup>d</sup> moiety, where R<sup>d</sup> is C<sub>1-4</sub>alkyl optionally substituted by hydroxy or C<sub>1-4</sub>alkoxy, and where R<sup>e</sup> is hydrogen, C<sub>1-4</sub>alkyl or benzyl;

or R<sup>11</sup>, R<sup>12</sup> and the nitrogen atom to which they are attached form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

or  $R^{11}$ ,  $R^{12}$  and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms to which is fused a benzene ring or a five membered or six membered nitrogen-containing heteroaromatic ring optionally containing 1, 2 or 3 additional heteroatoms selected from N, O and S;

5 Z represents a bond,  $C_{1-6}$ alkylene or  $C_{3-6}$ cycloalkylene;

n is zero, 1 or 2;

p is 1 or 2; and

q is 1 or 2;

and pharmaceutically acceptable salts thereof.

10 A preferred class of compounds of formula (I) is that wherein:

$R^7$  represents halogen, hydroxy,  $C_{2-4}$ alkenyl,  $N_3$ ,  $-NR^{11}R^{12}$ ,  $-NR^aCOR^b$ ,  $-OSO_2R^a$ ,  $-(CH_2)_pNR^a(CH_2)_qCOOR^b$  or a five membered or six membered nitrogen-containing heteroaromatic ring optionally containing 1, 2 or 3 additional heteroatoms selected from N, O and S which heteroaromatic ring is optionally substituted at any substitutable position by a substituent selected from =O, =S, halogen, hydroxy, -SH,  $COR^a$ ,  $CO_2R^a$ ,  $-ZNR^{11}R^{12}$ ,  $C_{1-4}$ alkyl, hydroxy $C_{1-4}$ alkyl, fluoro $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, fluoro $C_{1-4}$ alkoxy or  $C_{1-4}$ alkoxy substituted by a  $C_{1-4}$ alkoxy or hydroxyl group;

20  $R^{11}$  is hydrogen or  $C_{1-4}$ alkyl,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-4}$ alkyl, or  $C_{2-4}$ alkyl substituted by a  $C_{1-4}$ alkoxy or hydroxyl group;

$R^{12}$  is hydrogen or  $C_{1-4}$ alkyl,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-4}$ alkyl, or  $C_{2-4}$ alkyl substituted by a  $C_{1-4}$ alkoxy or hydroxyl group;

25 or  $R^{11}$ ,  $R^{12}$  and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy,  $COR^a$ ,  $CO_2R^a$  or  $C_{1-4}$ alkoxy optionally substituted by a  $C_{1-4}$ alkoxy or hydroxyl group, and said ring optionally containing a double bond, which ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or S(O)<sub>2</sub> or a second nitrogen atom which will be part of a NH or  $NR^d$  moiety where  $R^d$  is  $C_{1-4}$ alkyl optionally substituted by hydroxy or  $C_{1-4}$ alkoxy;

30 or  $R^{11}$ ,  $R^{12}$  and the nitrogen atom to which they are attached form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms; or a pharmaceutically acceptable salt thereof.

A further preferred class of compounds of formula (I) is that wherein  $R^1$  is hydrogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, halogen or  $CF_3$ .

Another preferred class of compounds of formula (I) is that wherein  $R^2$  is hydrogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, halogen or  $CF_3$ .

Also preferred is the class of compounds of formula (I) wherein  $R^3$  is hydrogen, fluorine, chlorine or  $CF_3$ .

5 A particularly preferred class of compounds of formula (I) is that wherein  $R^1$  is fluorine, chlorine or  $CF_3$ .

Another particularly preferred class of compounds of formula (I) is that wherein  $R^2$  is hydrogen, fluorine, chlorine or  $CF_3$ .

10 Also particularly preferred is the class of compounds of formula (I) wherein  $R^3$  is hydrogen, fluorine, chlorine or  $CF_3$ .

Preferably  $R^1$  and  $R^2$  are in the 3 and 5 positions of the phenyl ring.

More preferably  $R^1$  is 3-fluoro or 3- $CF_3$ .

More preferably  $R^2$  is 5-fluoro or 5- $CF_3$ .

More preferably  $R^3$  is hydrogen.

15 Most preferably  $R^1$  is 3-F or 3- $CF_3$ ,  $R^2$  is 5- $CF_3$  and  $R^3$  is hydrogen.

A further preferred class of compound of formula (I) is that wherein  $R^4$  is hydrogen.

Another preferred class of compounds of formula (I) is that wherein  $R^5$  is hydrogen, fluorine, chlorine or  $CF_3$ .

20 Preferably  $R^4$  is hydrogen and  $R^5$  is hydrogen or 4-fluoro.

$R^6$  is preferably  $C_{1-4}$ alkyl optionally substituted by hydroxy. In particular,  $R^6$  is preferably a methyl or hydroxymethyl group.

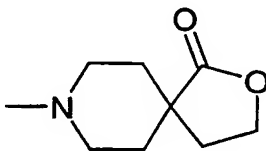
Where  $-NR^{11}R^{12}$  is defined as a substituent  $R^7$  or as a substituent on a heteroaromatic ring in the definition of  $R^7$ , then  $R^{11}$  may aptly be a  $C_{1-4}$ alkyl group or a  $C_{2-4}$ alkyl group substituted by a hydroxyl or  $C_{1-2}$ alkoxy group,  $R^{12}$  may aptly be a  $C_{1-4}$ alkyl group or a  $C_{2-4}$ alkyl group substituted by a hydroxyl or  $C_{1-2}$ alkoxy group, or  $R^{11}$  and  $R^{12}$  may be linked so that, together with the nitrogen atom to which they are attached, they form an azetidiny, pyrrolidinyl, piperidinyl, morpholino, thiomorpholino, piperazino or piperazino group  
25 substituted on the nitrogen atom by a  $C_{1-4}$ alkyl group or a  $C_{2-4}$ alkyl group substituted by a hydroxy or  $C_{1-2}$ alkoxy group. Particularly preferred heteroaliphatic rings formed by  $-NR^{11}R^{12}$  are azetidine, pyrrolidine, piperidine, morpholine, piperazine and N-methylpiperazine, and especially piperidine.  
30

Where the group  $\text{NR}^{11}\text{R}^{12}$  represents a heteroaliphatic ring of 4 to 7 ring atoms substituted by two groups, the first substituent, where present, is preferably selected from hydroxy,  $\text{CO}_2\text{R}^e$  (where  $\text{R}^e$  is hydrogen, methyl, ethyl or benzyl), or  $\text{C}_{1-2}$ alkyl substituted by hydroxy. Where present, the second

5 substituent is preferably a methyl group. Where two substituents are present, said substituents are preferably attached to the same carbon atom of the heteroaliphatic ring.

Where the group  $\text{NR}^{11}\text{R}^{12}$  represents a heteroaliphatic ring of 4 to 7 ring atoms substituted by a spiro-fused lactone ring, a particularly preferred example

10 is:



Where the group  $\text{NR}^{11}\text{R}^{12}$  represents a heteroaliphatic ring of 4 to 7 ring atoms and said ring contains a double bond, a particularly preferred group is 3-pyrroline.

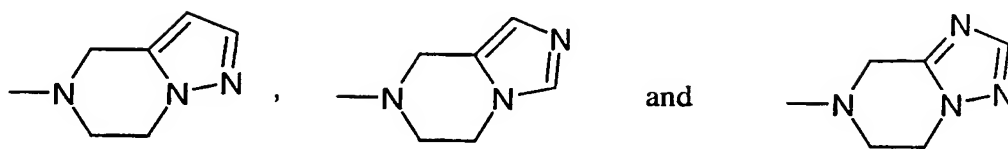
Where the group  $\text{NR}^{11}\text{R}^{12}$  represents a non-aromatic azabicyclic ring system, such a system may contain between 6 and 12, and preferably between 7 and 10, ring atoms. Suitable rings include 5-azabicyclo[2.1.1]hexyl,

15 5-azabicyclo[2.2.1]heptyl, 6-azabicyclo[3.2.1]octyl, 2-azabicyclo[2.2.2]octyl, 6-azabicyclo[3.2.2]nonyl, 6-azabicyclo[3.3.1]nonyl, 6-azabicyclo[3.3.2]decyl,

20 7-azabicyclo[4.3.1]decyl, 7-azabicyclo[4.4.1]undecyl and 8-azabicyclo[5.4.1]dodecyl, especially 5-azabicyclo[2.2.1]heptyl and 6-azabicyclo[3.2.1]octyl.

Where the group  $\text{NR}^{11}\text{R}^{12}$  represents a heteroaliphatic ring of 4 to 7 ring atoms to which is fused a benzene ring or a five membered or six membered

25 nitrogen-containing heteroaromatic ring optionally containing 1, 2 or 3 additional heteroatoms selected from N, O and S, said heteroaromatic ring is preferably a five-membered ring, in particular a pyrrole, imidazole or triazole ring, a nitrogen atom of which is preferably included in the heteroaliphatic ring. Suitable examples of such fused ring systems include



Particularly suitable moieties  $\text{NR}^{11}\text{R}^{12}$  include those wherein  $\text{NR}^{11}\text{R}^{12}$  is amino, methylamino, dimethylamino, diethylamino, azetidino, pyrrolidino, piperidino, morpholino and piperazino.

5 Where  $\text{R}^7$  represents an optionally substituted five or six-membered nitrogen-containing heteroaromatic ring optionally containing 1, 2 or 3 additional heteroatoms selected from N, O and S, the heteroaromatic ring is selected from pyrrole, pyridine, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyrazine, pyrimidine, pyridazine, triazole, oxadiazole, thiadiazole, triazine, and  
10 tetrazole.

Preferred compounds of the present invention are those wherein  $\text{R}^7$  is a group selected from imidazole, 1,2,3-triazole and 1,2,4-triazole.

Particularly preferred compounds of the present invention are those wherein  $\text{R}^7$  is a group selected from imidazol-1-yl and 1,2,4-triazol-1-yl.

15 Where  $\text{R}^7$  represents an optionally substituted five membered or six membered nitrogen-containing heteroaromatic ring, preferred substituents are  $-\text{ZNR}^{11}\text{R}^{12}$  and  $\text{C}_{1-2}$ alkyl (especially methyl). With reference to the group  $\text{ZNR}^{11}\text{R}^{12}$  defined as a substituent on a heteroaromatic ring in the definition of  $\text{R}^7$ , Z may be a bond or a linear, branched or cyclic group. Favourably Z is a bond  
20 or contains 1 to 4 carbon atoms and most favourably 1 to 2 carbon atoms. A particularly favourable group Z is  $-\text{CH}_2-$ . In this instance, particularly suitable moieties  $\text{NR}^{11}\text{R}^{12}$  include those wherein  $\text{NR}^{11}\text{R}^{12}$  is amino, methylamino, dimethylamino, diethylamino, azetidino, pyrrolidino, piperidino, morpholino and piperazino. Most especially,  $-\text{ZNR}^{11}\text{R}^{12}$ , as a substituent on a heteroaromatic  
25 ring in the definition of  $\text{R}^7$ , is preferably  $\text{CH}_2\text{N}(\text{CH}_3)_2$ .

A further preferred class of compound of formula (I) is that wherein  $\text{R}^7$  represents halogen (especially iodine), hydroxy, vinyl,  $\text{N}_3$  or  $-\text{OSO}_2\text{R}^a$  (especially where  $\text{R}^a$  is methyl).

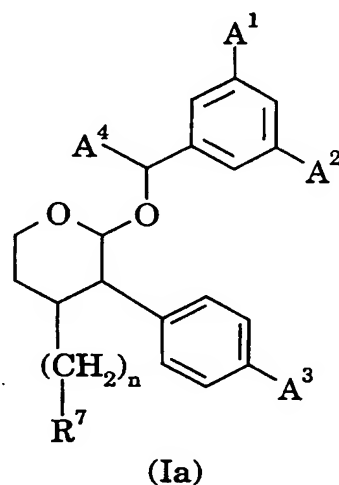
30 Another preferred class of compound of formula (I) is that wherein  $\text{R}^8$  is hydrogen or methyl, and especially hydrogen.



A further preferred class of compound of formula (I) is that wherein  $n$  is 1 or 2, and especially wherein  $n$  is 1.

Another preferred class of compound of formula (I) is that wherein one of  $R^9$  and  $R^{10}$  is hydrogen, and especially wherein  $R^9$  and  $R^{10}$  are both hydrogen atoms.

One favoured group of compounds of the present invention are of the formula (Ia) and pharmaceutically acceptable salts thereof:



wherein

$A^1$  is fluorine or  $CF_3$ ;

$A^2$  is fluorine or  $CF_3$ ;

$A^3$  is fluorine or hydrogen;

$A^4$  is methyl or hydroxymethyl; and

$R^7$  and  $n$  are as defined in relation to formula (I).

When any variable occurs more than one time in formula (I) or in any substituent, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "alkyl" or "alkoxy" as a group or part of a group means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy.

As used herein, the terms "fluoroC<sub>1-6</sub>alkyl" and "fluoroC<sub>1-6</sub>alkoxy" means a C<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxy group in which one or more (in particular, 1 to 3) hydrogen atoms have been replaced by fluorine atoms. Similarly, the term "fluoroC<sub>1-4</sub>alkyl" means a C<sub>1-4</sub>alkyl group in which one or more (in particular 1 to 3) hydrogen atoms have been replaced by fluorine atoms. Particularly preferred are fluoroC<sub>1-3</sub>alkyl and fluoroC<sub>1-3</sub>alkoxy groups, for example, CF<sub>3</sub>, CH<sub>2</sub>CH<sub>2</sub>F, CH<sub>2</sub>CHF<sub>2</sub>, CH<sub>2</sub>CF<sub>3</sub>, OCF<sub>3</sub>, OCH<sub>2</sub>CH<sub>2</sub>F, OCH<sub>2</sub>CHF<sub>2</sub> or OCH<sub>2</sub>CF<sub>3</sub>, and most especially CF<sub>3</sub>, OCF<sub>3</sub> and OCH<sub>2</sub>CF<sub>3</sub>.

The cycloalkyl groups referred to herein may represent, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. A suitable cycloalkylalkyl group may be, for example, cyclopropylmethyl.

Similarly cycloalkoxy groups referred to herein may represent, for example, cyclopropoxy or cyclobutoxy.

As used herein, the terms "alkenyl" and "alkynyl" as a group or part of a group means that the group is straight or branched. Examples of suitable alkenyl groups include vinyl and allyl. A suitable alkynyl group is propargyl.

When used herein the term "halogen" means fluorine, chlorine, bromine and iodine. The most apt halogens are fluorine and chlorine of which fluorine is preferred, unless otherwise stated.

Specific compounds within the scope of this invention include:

(2R,3S,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-3-phenyl-4-vinyltetrahydropyran;

(2R,3R,4S,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-3-phenyl-4-vinyltetrahydropyran;

(2R,3S,4S,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-hydroxymethyl-3-phenyltetrahydropyran;

(2R,3S,4S,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(methanesulfonyloxy)methyl-3-phenyltetrahydropyran;

(2RS,3SR,4SR,8RS)-4-azidomethyl-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-3-phenyltetrahydropyran;

(2RS,3SR,4SR,8RS)-4-aminomethyl-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-3-phenyltetrahydropyran;

(2RS,3SR,4SR,8RS)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(dimethylamino)methyl-3-phenyltetrahydropyran;

- (2R,3S,4S,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(pyrrolidin-1-yl)methyl-3-phenyltetrahydropyran;  
(2R,3S,4S,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(1,2,4-triazol-1-yl)methyl-3-phenyltetrahydropyran;  
5 (2R,3S,4S,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(2-hydroxyethyl)-3-phenyltetrahydropyran;  
(2R,3S,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(2-methanesulfonyloxy)ethyl-3-phenyltetrahydropyran;  
(2R,3R,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-  
10 hydroxymethyl-3-phenyltetrahydropyran;  
(2R,3R,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(methanesulfonyloxy)methyl-3-phenyltetrahydropyran;  
(2R,3R,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(2-hydroxyethyl)-3-phenyltetrahydropyran;  
15 (2R,3R,4S,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(2-methanesulfonyloxy)ethyl-3-phenyltetrahydropyran;  
and pharmaceutically acceptable salts thereof.

Further specific compounds of the present invention include:

- (2R,3S,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(2-iodoethyl)-3-  
20 phenyltetrahydropyran;  
(2R,3R,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(iodomethyl)-3-phenyltetrahydropyran;  
(2R,3R,4S,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(2-iodoethyl)-3-phenyltetrahydropyran;  
25 (2R,3S,4S,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-formyl-3-phenyltetrahydropyran;  
(2R,3S,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(2-formylmethyl)-3-phenyltetrahydropyran;  
(2R,3R,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-formyl-3-  
30 phenyltetrahydropyran;  
(2R,3S,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-carboxymethyl-3-phenyltetrahydropyran;  
(2R,3R,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-carboxy-3-phenyltetrahydropyran;

- (2R,3R,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(4-methyl-4-carboxypiperidin-1-yl)methyl-3-phenyltetrahydropyran;
- (2R,3R,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(4-ethoxycarbonylpiperidin-1-yl)methyl-3-phenyltetrahydropyran;
- 5 (2R,3R,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(4-carboxypiperidin-1-yl)methyl-3-phenyltetrahydropyran;
- (2R,3R,4R,8R,9(3'R))-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-ethoxycarbonyl-3-methylpiperidin-1-yl)methyl-3-phenyltetrahydropyran;
- (2R,3R,4R,8R,9(3'S))-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-ethoxycarbonyl-3-methylpiperidin-1-yl)methyl-3-phenyltetrahydropyran;
- 10 (2R,3R,4R,8R,9(3'R))-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-carboxy-3-methylpiperidin-1-yl)methyl-3-phenyltetrahydropyran;
- (2R,3R,4R,8R,9(3'S))-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-carboxy-3-methylpiperidin-1-yl)methyl-3-phenyltetrahydropyran;
- 15 (2R,3R,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-3-phenyl-4-(1,2,4-triazol-3-yl)methyltetrahydropyran;
- (2R,3S,4S,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-3-phenyl-4-(1,2,4-triazol-3-yl)methyltetrahydropyran;
- (2R,3R,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-3-phenyl-4-(5-methoxycarbonyl-1,2,3-triazol-1-yl)ethyltetrahydropyran;
- 20 (2R,3R,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(4-methoxycarbonyl-1,2,3-triazol-1-yl)ethyl-3-phenyltetrahydropyran;
- and pharmaceutically acceptable salts thereof.

In a further aspect of the present invention, the compounds of formula (I)

25 may be prepared in the form of a pharmaceutically acceptable salt, especially an acid addition salt.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic

30 pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic

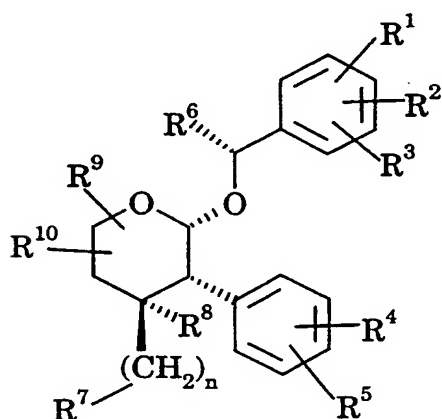
acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

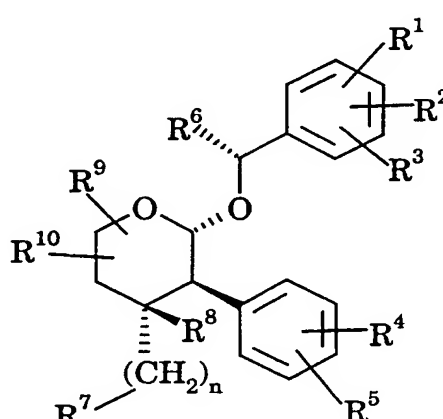
The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The compounds according to the invention have at least three asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The preferred compounds of the formula (I) and (Ia) will have the stereochemistry of the 2-, 3-, 4- and 8-positions as shown in formulae (Ib) and (Ic)



(Ib)



(Ic)

It will be appreciated that the preferred definitions of the various substituents recited herein may be taken alone or in combination and, unless

otherwise stated, apply to the generic formula for compounds of the present invention as well as to the preferred classes of compound represented by formula (Ia), formula (Ib) and formula (Ic).

5 The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) in association with a pharmaceutically acceptable carrier or excipient.

10 Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation. Oral compositions such as tablets, pills, capsules or wafers are particularly preferred.

15 For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active  
20 ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets  
25 or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to  
30 be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or  
5 peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Preferred compositions for administration by injection include those  
10 comprising a compound of formula (I), as the active ingredient, in association with a surface-active agent (or wetting agent or surfactant) or in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or  
15 mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be  
20 breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

25 The present invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide  
30 variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity.

Thus, for example, compounds of formula (I) are of use in the treatment or prevention of a variety of disorders of the central nervous system. Such disorders include mood disorders, such as depression or more particularly

depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety disorders; schizophrenia and other psychotic disorders, for example, schizophreniform disorders, schizoaffective disorders, delusional disorders, brief psychotic disorders, shared psychotic disorders and psychotic disorders with delusions or hallucinations; delirium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeldt-Jakob disease, or due to multiple aetiologies; Parkinson's disease and other extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremour; substance-related disorders arising from the use of alcohol, amphetamines (or amphetamine-like substances) caffeine, cannabis, cocaine, hallucinogens, inhalants and aerosol propellants, nicotine, opioids, phenylglycidine derivatives, sedatives, hypnotics, and anxiolytics, which substance-related disorders include dependence and abuse, intoxication, withdrawal, intoxication delirium, withdrawal delirium, persisting dementia, psychotic disorders, mood disorders, anxiety disorders, sexual dysfunction and sleep disorders; epilepsy; Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, for example diabetic and chemotherapy-induced neuropathy, and postherpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia and other neuralgias; and cerebral vascular disorders due to acute or chronic cerebrovascular damage such as cerebral infarction, subarachnoid haemorrhage or cerebral oedema.



Tachykinin, and in particular substance P, activity is also involved in nociception and pain. The compounds of the present invention will therefore be of use in the prevention or treatment of diseases and conditions in which pain predominates, including soft tissue and peripheral damage, such as acute

5 trauma, osteoarthritis, rheumatoid arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, myofascial pain syndromes, headache, episiotomy pain, and burns; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example, odontalgia, abdominal pain, gynaecological pain, for example, dysmenorrhoea, and labour pain; pain associated with nerve

10 and root damage, such as pain associated with peripheral nerve disorders, for example, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis; pain associated with carcinoma, often referred to as cancer pain; central nervous system pain, such as pain due to spinal cord or brain stem

15 damage; low back pain; sciatica; ankylosing spondylitis, gout; and scar pain.

The compounds of formula (I) may also be of use in the treatment of respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, bronchopneumonia, chronic

20 bronchitis, cystic fibrosis and asthma, adult respiratory distress syndrome, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis, pruritis and sunburn; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; ophthalmic conditions associated with cell proliferation such as proliferative

25 vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis.

The compounds of formula (I) may also be of use in the treatment of neoplasms, including breast tumours, neuroganglioblastomas and small cell carcinomas such as small cell lung cancer.

30 The compounds of formula (I) may also be of use in the treatment of gastrointestinal (GI) disorders, including inflammatory disorders and diseases of the GI tract such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the neuronal control of viscera, ulcerative colitis, Crohn's disease, irritable bowel syndrome and emesis, including acute,

delayed or anticipatory emesis such as emesis induced by chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, for example, motion sickness, vertigo, dizziness and Meniere's disease, surgery, migraine, variations in intracranial pressure, gastro-oesophageal reflux disease, acid indigestion, over indulgence in food or drink, acid stomach, waterbrash or regurgitation, heartburn, for example, episodic, nocturnal or meal-induced heartburn, and dyspepsia.

The compounds of formula (I) may also be of use in the treatment of a variety of other conditions including stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; plasma extravasation resulting from cytokine chemotherapy, disorders of bladder function such as cystitis, bladder detrusor hyper-reflexia and incontinence; fibrosing and collagen diseases such as scleroderma and eosinophilic fasciitis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, vascular headache, migraine and Reynaud's disease; pain or nociception attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine; obesity; bulimia nervosa; and compulsive eating disorders.

The compounds of formula (I) are also of value in the treatment of a combination of the above conditions, in particular in the treatment of combined post-operative pain and post-operative nausea and vomiting.

The present invention further provides a compound of formula (I) for use in therapy.

According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

According to a further aspect of the present invention, it may be desirable to treat any of the aforementioned conditions with a combination of a compound according to the present invention and one or more other pharmacologically active agents suitable for the treatment of the specific condition. The compound  
5 of formula (I) and the other pharmacologically active agent(s) may be administered to a patient simultaneously, sequentially or in combination.

The excellent pharmacological profile of the compounds of the present invention offers the opportunity for their use in therapy at low doses thereby minimising the risk of unwanted side effects.

10 In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day.

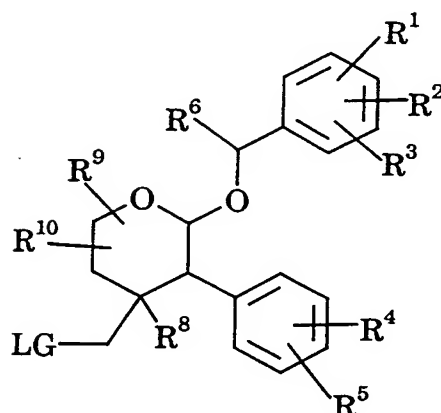
For example, in the treatment of conditions involving the  
15 neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of emesis, a suitable dosage level is about 0.001 to 10  
20 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 3 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of psychiatric disorders, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and  
25 especially 0.01 to 3 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the  
30 nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

According to a general process (A), compounds of formula (I), in which n is 1, may be prepared by the reaction of a compound of formula (II)



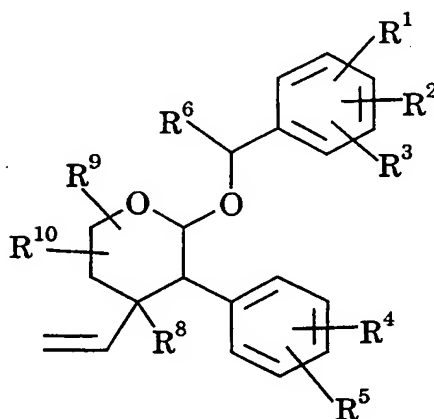
(II)

wherein LG is a suitable leaving group such as an alkyl- or arylsulfonyloxy group (e.g. mesylate or tosylate) or a halogen atom (e.g. bromine, chlorine or iodine); by  
 5 reaction with an appropriate amine of the formula  $\text{HNR}^{11}\text{R}^{12}$ , or a heteroaromatic compound suitable for the addition of a five or six-membered nitrogen containing heteroaromatic ring as defined in relation to formula (I), or an azide such as sodium azide.

In each case, the reaction is preferably effected at an elevated  
 10 temperature, for example, between 40°C and 80°C, especially between 50°C and 60°C. The reaction with a heteroaromatic compound is preferably effected in the presence of a suitable organic solvent such as dimethylformamide. The reaction with an azide is preferably effected in the presence of dimethylsulfoxide.

A particularly preferred compound of formula (II) is that wherein the  
 15 group LG is mesylate - i.e. a compound of formula (I) in which R<sup>7</sup> is the group -OSO<sub>2</sub>CH<sub>3</sub>.

According to another general process (B), compounds of formula (I), in  
 which R<sup>7</sup> is hydroxy and n is 1 or 2, may be prepared by the interconversion of a  
 corresponding compound of formula (I) in which n is zero and R<sup>7</sup> is vinyl,  
 20 hereinafter referred to as formula (III)

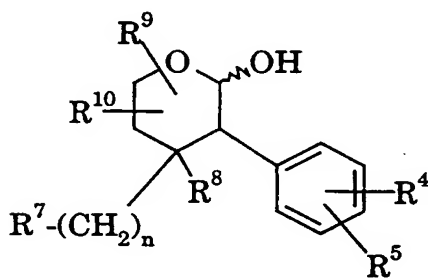


(III)

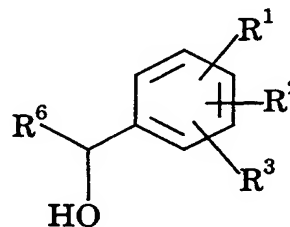
by reaction with ozone, followed by a reaction with a reducing agent such as sodium borohydride ( $n$  is 1), or by reaction with a reducing agent such as  
 5 borane.tetrahydrofuran complex, followed by hydrogen peroxide in the presence of a base such as sodium hydroxide.

According to another general process (C), compounds of formula (I) may be prepared by the reaction of a compound of formula (IV) with a compound of formula (V)

10



(IV)

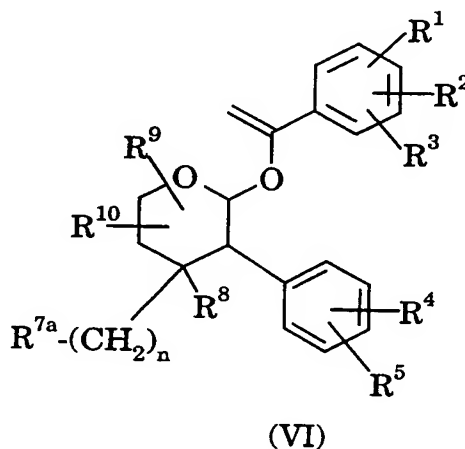


(V)

preferably in the presence of a resin catalyst such as Amberlyst™ 15, and 3 Angstrom molecular sieves.

15 The reaction is conveniently effected in a suitable solvent such as a halogenated hydrocarbon, for example, dichloromethane, conveniently at room temperature.

According to another general process (D), compounds of formula (I), in which  $R^6$  is either methyl or hydroxymethyl, may be prepared by the reaction of a compound of formula (VI)



5

wherein  $R^{7a}$  is as defined for  $R^7$  in relation to formula (I) or, more preferably, is a precursor therefor; under either:

- (a) (where  $R^6$  is methyl) catalytic hydrogenation conditions (e.g.  $H_2$ ,  $Pd(OH)_2$  on carbon) in a suitable solvent such as an ester, for example, ethyl acetate; or
- (b) (where  $R^6$  is hydroxymethyl) reducing conditions (e.g. borane or  $BH_3 \cdot THF$ ) followed by treatment with hydrogen peroxide and a base such as sodium hydroxide, conveniently in a solvent such as an ether, for example, tetrahydrofuran.

15

Where  $R^{7a}$  is a precursor group (such as a TBDMS-protected hydroxyl group) deprotection is conveniently effected by treatment with an organic acid such as tetrabutylammonium fluoride.

Further details of suitable procedures will be found in the accompanying Examples.

20

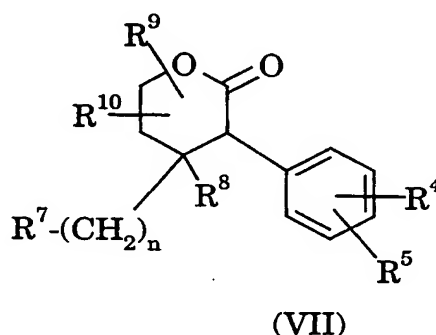
Compounds of formula (II) may be prepared by conventional methods from, for example, a corresponding compound of formula (I) in which  $R^7$  is a hydroxyl group. Thus, for example, when LG is a mesylate group a corresponding compound of formula (I) in which  $R^7$  is hydroxyl may be reacted with methanesulfonyl chloride in the presence of a base, such as triethylamine.

25

The reaction is conveniently effected in a solvent such as a halogenated hydrocarbon, for example, dichloromethane.

Compounds of formula (III) may be prepared, for example, by the method of general process (C), above

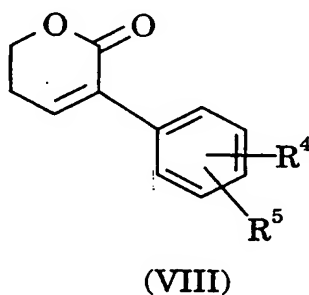
- 5      Compounds of formula (IV) may be prepared by the reduction of a compound of formula (VII)



- 10      using conventional conditions such as sodium borohydride in the presence of a transition metal catalyst such as cerium chloride hexahydrate, in a solvent such as alcohol, for example, ethanol; or using DiBAL in a solvent such as a halogenated hydrocarbon, for example, dichloromethane.

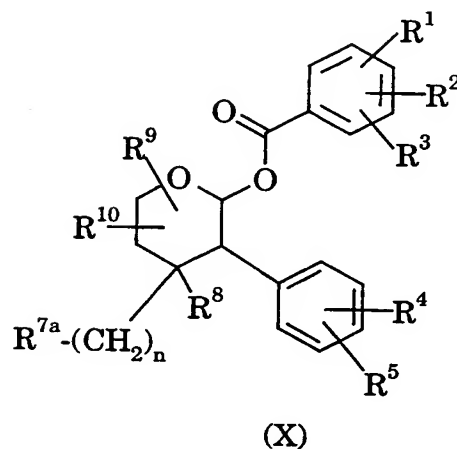
Compounds of formula (VII) in which R<sup>7</sup> is vinyl, R<sup>8</sup> is hydrogen and n is 1 may be prepared from a compound of formula (VIII)

15



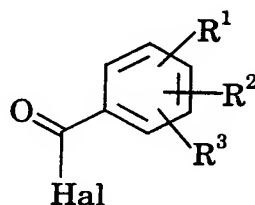
- 20      by reaction with a vinyl Grignard reagent such as vinylMgBr, preferably in the presence of copper(I)iodide, and a suitable solvent such as an ether, for example, tetrahydrofuran. This reaction is effected at reduced temperature, for example, below -40°C and preferably at -78°C.

Compounds of formula (VI) may be prepared by the reaction of a compound of formula (X)



with dimethyltitanocene in a solvent such as toluene, pyridine or  
 5 tetrahydrofuran, or a mixture thereof.

Compounds of formula (X) may be prepared by the reaction of a compound  
 of formula (VII) with L-Selectride™ (lithium tri-*sec*-butylborohydride) followed by  
 treatment with a compound of formula (XI)



10 (XI)

wherein Hal is a halogen atom, preferably chlorine.

Compounds of formula (V), (VIII) and (XI) are either known compounds or  
 may be prepared by methods analogous to those described herein.

It will be appreciated that the general methodology described above may  
 15 be adapted, using methods that are readily apparent to one of ordinary skill in  
 the art, in order to prepare further compounds of the present invention.

During any of the above synthetic sequences it may be necessary and/or  
 desirable to protect sensitive or reactive groups on any of the molecules  
 concerned. This may be achieved by means of conventional protecting groups,  
 20 such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W.



McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

5           The exemplified compounds of this invention were tested by the methods set out at pages 36 to 39 of International Patent Specification No. WO 93/01165. The compounds were found to be active with IC<sub>50</sub> at the NK<sub>1</sub> receptor of less than 100nM on said test method.

10           The following non-limiting Examples serve to illustrate the preparation of compounds of the present invention:

### DESCRIPTION 1

#### 3-Phenyl-4-vinyl-3,4,5,6-tetrahydropyran-2-one

15           Vinylmagnesium bromide (77ml, 1M THF) was added to a slurry of copper (I) iodide (7.37g) in tetrahydrofuran (80ml) at -78°C under a nitrogen atmosphere. This mixture was stirred at -40°C for 30 minutes, then re-cooled to -78°C. A solution of 3-phenyl-5,6-dihydro-2-pyrone (*J. Org. Chem.* 1967, 32, 2354) (4.6g) and chlorotrimethylsilane (3.28ml) in THF (80ml) was added to the stirred mixture. Thin layer chromatography showed all starting material had reacted.

20           The mixture was quenched with ammonium chloride (saturated aqueous solution) at -78°C and the resulting mixture was allowed to come to room temperature and was stirred for 2 hours until the aqueous layer became dark blue. The mixture was filtered through Celite™ to remove any insoluble inorganics and the solution was extracted with ethyl acetate (3x100ml). The

25           pooled organic extracts were washed with brine, dried (MgSO<sub>4</sub>) and concentrated to give a yellow oil. This was purified on silica using 30-40% ether in hexane as eluant to afford the title compound (4.9g, crystallised on standing) as a mixture of *cis* and *trans* isomers (2:1). Recrystallisation of this mixture from ether-hexane afforded the pure *cis* isomer as white prisms.

30           Signals for the *cis* lactone: <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.95-2.15 (2H, m), 2.91-3.00 (1H, m), 3.51 (1H, d, J 5.8Hz), 4.59-4.65 (2H, m), 4.93-5.00 (2H, m), 5.48-5.58 (1H, m), 7.17-7.19 (2H, m), 7.26-7.35 (3H, m).

Signals for the *trans* lactone:  $^1\text{H}$  NMR (360MHz,  $\text{CDCl}_3$ )  $\delta$  1.89-1.99 (1H, m), 2.10-2.18 (1H, m), 2.79-2.85 (1H, m), 3.51 (1H, d, J 10.3Hz), 4.43-4.57 (2H, m), 4.90-5.01 (2H, m), 5.66 (1H, hept, J 17.2, 10.4, 7.0Hz), 7.16-7.20 (2H, m), 7.23-7.36 (3H, m).

5

## DESCRIPTION 2

### ***trans* 3-Phenyl-4-vinyl-3,4,5,6-tetrahydropyran-2-one**

A mixture of *cis*- and *trans*-3-phenyl-4-vinyl-5,6-dihydropyran-2-one (Description 1; 5.25g; ratio 2:1) in tetrahydrofuran (10ml) was heated in an oil bath (80°C) with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.2g) for 30 minutes. The cooled solution was evaporated *in vacuo* and a solution of the residue in dichloromethane (50ml) was filtered through a pad of silica gel. After washing the silica with dichloromethane (50ml), the combined filtrate was evaporated to dryness (4.8g, *cis:trans* ratio 1:19) and used without further purification.

$^1\text{H}$  NMR (360MHz,  $\text{CDCl}_3$ )  $\delta$  1.99-1.89 (1H,m), 2.18-2.10(1H,m), 2.88-2.79(1H,m), 3.50(1H, d J 10.3Hz), 4.57-4.443(2H,m), 5.03-4.90(2H,m), 5.71-5.63(1H,m), 7.36-7.16(5H,m).

10

15

## DESCRIPTION 3

### ***trans* 3-Phenyl-4-vinyl-tetrahydropyran-2-ol**

To a cooled (-30°C) solution of *trans* 3-phenyl-4-vinyl-5,6-dihydropyran-2-one (Description 2; 0.97g) in ethanol (21ml) was added a solution of cerium chloride hexahydrate (1.79g) in water (7ml) followed by a slow addition of sodium borohydride (0.18g) (so as to maintain an internal temperature of -20°C to -30°C). After stirring the solution for 30 minutes at -30°C acetone (2ml) was added. The solution was evaporated and the residue partitioned between ethyl acetate and water. The organic phase was dried ( $\text{MgSO}_4$ ) and evaporated to dryness (0.92g) giving a mixture of 2,3-*cis:trans* lactol isomers (approximately 30:70 by NMR).

$^1\text{H}$  NMR (360MHz,  $\text{CDCl}_3$ )  $\delta$  1.67-1.80(m), 2.35(d J 2.0Hz), 2.38(1.6H, dd J 11.4Hz and 8.3Hz), 2.6(1.9H, m), 2.8(dd J 12.0Hz and 2.7Hz), 3.2(m), 3.75(m) 4.15(m), 4.24(dd J 12.2Hz and 3.0Hz), 4.78-4.87(m), 4.95(dt J 17.2Hz and 1.36Hz), 5.20(dd J 5.8Hz and 2.9Hz), 5.46-5.57(m), 7.18-7.34(m).

25

30

## DESCRIPTION 4

**Benzyl 4-methylpiperidine-4-carboxylate**(i) N-Butoxycarbonylpiperidine-4-carboxylic acid

- 5 Isonipecotic acid (6.42g) was dissolved in a 4:1 mixture of tetrahydrofuran:water (100ml), potassium carbonate (10.3g) and di-tert-butyl dicarbonate (11.4g) were added and stirred at room temperature over night. The tetrahydrofuran was removed *in vacuo* and the residue dispersed between water (100ml) and ethyl acetate (100ml), the aqueous phase was extracted with ethyl acetate (3x75ml).
- 10 The combined organics were washed with brine and dried (MgSO<sub>4</sub>). The solution was filtered, evaporated to dryness to afford a white solid of N-butoxycarbonylpiperidine-4-carboxylic acid(11.6g).
- <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.46(9H, s), 1.58-1.71(2H, m), 1.87-1.95(2H, m), 2.45-2.53(1H, m), 2.81-2.90(2H, m), 3.97-4.04(2H, m).

15

(ii) Benzyl N-butoxycarbonylpiperidine-4-carboxylate

- N-Butoxycarbonyl-4-piperidinecarboxylic acid (4.6g) was dissolved in dimethylformamide (20ml) and placed under an atmosphere of nitrogen. Benzyl bromide (2.9ml) and potassium carbonate (8.3g) were added and heated at 60°C
- 20 for 3 hours. The dimethylformamide was removed *in vacuo* and azeotroped with toluene (three times). The residue was dispersed between ethyl acetate and water and the aqueous phase was extracted with ethyl acetate (3x100ml). The combined organic phases were washed with brine and dried (MgSO<sub>4</sub>). The solution was filtered, evaporated to dryness and the residue was purified by
- 25 chromatography on silica gel (eluting with isohexane containing increasing concentrations amounts of ethyl acetate 5-30%) to give benzyl N-butoxycarbonylpiperidine-4-carboxylate as a clear oil (7.68g).
- <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 1.45(9H, s), 1.61-1.70(2H, m), 1.87-1.94(2H,m), 2.45-2.53(1H,m), 2.77-2.87(2H, m), 2.96-4.06(2H, m), 5.13(2H, s)7.28-7.38(5H, m).

30

(iii) Benzyl N-butoxycarbonyl-4-methylpiperidine-4-carboxylate

The benzyl ester (5.18g) was dissolved in tetrahydrofuran (40ml) under an atmosphere of nitrogen and cooled to -78°C, potassium bis(trimethylsilyl)amide

(32.5ml 0.5M in toluene) was added dropwise keeping the internal temperature below  $-60^{\circ}\text{C}$ . The reaction was stirred at  $-78^{\circ}\text{C}$  for 15 minutes, methyl iodide (2.5ml) was added and the temperature was allowed to warm to room temperature. Water (5ml) was added, the solvent was removed *in vacuo*, and the  
5 residue was dispersed between ethyl acetate (100ml) and water (100ml). The aqueous layer was extracted with ethyl acetate (3x60ml), the combined organics were washed with brine and dried over  $\text{MgSO}_4$ . The solution was filtered, evaporated to dryness and the residue was purified by chromatography on silica gel (eluting with isohexane containing increasing concentrations of ethyl acetate  
10 2.5-5%) to give a clear oil (3.4g).

$^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  1.22(3H, s), 1.33-1.42(2H, m), 1.44(9H, s), 2.05-2.12(2H, m), 2.95-3.03(2H, m), 3.68-3.78(2H, m), 5.14(2H, s), 7.30-7.39(5H, m).

(iv) Benzyl 4-methylpiperidine-4-carboxylate

15 The Boc-protected amine (2.8g) was dissolved in dichloromethane (4ml) and cooled to  $0^{\circ}\text{C}$ , trifluoroacetic acid (2ml) was added dropwise and the reaction allowed to warm to room temperature. After 1 hour the solvent was removed *in vacuo* and the residue dispersed between ethyl acetate (50ml) and sat.  $\text{K}_2\text{CO}_3$  (50ml). The aqueous layer was extracted with ethyl acetate (3x30ml), the  
20 combined organics were washed with brine and dried over  $\text{MgSO}_4$ . The solution was filtered, evaporated to dryness to afford a white solid (1.91g).

MS  $m/z$  ( $\text{ES}^+$ ) 234 ( $\text{M}+\text{H}$ ).

$^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  1.22(3H, s), 1.40(2H, ddd J 10Hz 10 Hz 3.9Hz), 1.98(1H, s), 2.10(2H, dm J 16.5Hz), 2.67(2H, ddd J 10.3Hz 10.3Hz 2.8Hz),  
25 2.91(2H, m), 5.14(2H, s), 7.28-7.39(5H, m).

**EXAMPLE 1**

(2R,3S,4R,8R)-2-(1-(1-(3,5-Bis(trifluoromethyl)phenyl)ethyl)oxy)-3-phenyl-4-vinyltetrahydropyran; and

30 (2R,3R,4S,8R)-2-(1-(1-(3,5-Bis(trifluoromethyl)phenyl)ethyl)oxy)-3-phenyl-4-vinyltetrahydropyran

A solution of the mixture of lactol isomers of *trans* 3-phenyl-4-vinyltetrahydropyran-2-ol (Description 3; 15.8g) and (R)-1-(3,5-

bis(trifluoromethyl)phenyl)ethanol (20g) in dichloromethane (200ml) was stirred with Amberlyst™ 15 resin (5g) and 3Å molecular sieves (15g) for 72 hours. The solution was filtered, evaporated to dryness and the residue purified by column chromatography on silica gel (eluting with increasing amounts of

5 dichloromethane in isohexane, 0-20%).

isomer 1

(2R,3S,4R,8R) 3,4-*trans*-2,3-*cis* (earlier eluting) isomer: <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 1.45(3H, d J 6.6Hz), 1.75(1H, qd J 12.3Hz and 4.9Hz), 2.71(1H, dd J 12.0Hz and 3.1Hz), 3.14(1H,m), 3.76(1H, dd J 11.3Hz and 4.0Hz), 4.06(1H, td J 13.3Hz and 2.52Hz), 4.48(1H, d J 3.08Hz), 4.86(2H,m), 4.97(1H, d J 17.2Hz), 5.52(1H, m), 7.27-7.18(7H,m), 7.59(1H, s).

isomer 2 and 3

(approximately 1:1 mixture of isomers with undetermined relative stereochemistry): <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 1.00(3H, d J 6.5Hz), 1.07(3H, d J 6.4Hz), 1.72(4H, m), 2.55(1H, dd J 11.5Hz and 7.9Hz), 2.62(1H,m), 2.81(1H,dd J 12.0Hz and 3.2Hz), 3.02(1H,m), 3.60(2H,m), 3.75(1H, td J 11.3Hz and 3.8Hz), 4.07(1H, dm J approx. 11.4Hz), 4.59(1H, d J 8.0Hz), 4.67(1H, q J 6.41Hz), 4.73(1H, q J 6.4Hz), 4.82-4.97(5H,m), 5.47-5.57(2H,m), 7.20-7.65(12H,m), 7.65(2H,s), 7.71(1H,s), 7.77(2H,s), 7.78(1H,s).

20 isomer 4

(2R,3R,4S,8R) 3,4-*trans*-2,3-*trans* (later eluting) isomer: <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.36(3H, d J 6.6Hz), 1.73-1.67(2H, m), 2.55-2.42(2H, m), 3.62-3.55(1H,m), 4.13(1H, dt J 11.8Hz and 3.6Hz), 4.23(1H, d J 8.0Hz), 4.77(1H, d, J 2.2Hz), 4.81(1H, apparent s), 4.96(1H, q J 6.6Hz), 4.48(1H,m), 6.99-7.02(2H,m), 7.25-7.18(5H, m), 7.66(1H, s).

**EXAMPLE 2**

**(2R,3S,4S,8R)-2-(1-(1-(3,5-Bis(trifluoromethyl)phenyl)ethyl)oxy)-4-hydroxymethyl-3-phenyltetrahydropyran**

30 (2R,3S,4S,8R) 2-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl-1-oxy)-3-phenyl-4-vinyltetrahydropyran (3,4-*trans*-2,3-*cis* ; isomer1; Example 1; 3.95g) was dissolved in dichloromethane (40ml) and methanol (40ml). This solution was cooled to -78°C under an inert atmosphere and through the solution was bubbled

ozone until the solution produced a persistent blue colouration. The solution was then purged with nitrogen followed by careful addition of sodium borohydride (1.68g). The solution was stirred at room temperature for 1 hour and then evaporated to dryness. The residue was partitioned between ethyl acetate and water and the organic phase was washed further with brine and the dried (MgSO<sub>4</sub>). After removal of the solvent *in vacuo* the residue was purified by chromatography on silica (eluting with increasing concentrations (5-15%) of ethyl acetate in isohexane).

<sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.07 (1H, t, J 5.4Hz), 1.46 (3H, d, J 6.6Hz), 1.66-1.80 (1H, m), 1.92-2.00 (1H, m), 2.58-2.72 (1H, m), 2.75 (1H, dd, J 12.0, 3.0Hz), 3.27-3.32 (1H, m), 3.48-3.52 (1H, m), 3.79 91H, dd, J 11.1, 3.6Hz), 4.06 (1H, t app, J 10.8Hz), 4.46 (1H, d, J 3.1Hz), 4.89 (1H, q, J 6.6Hz), 7.22 (2H, s), 7.25-7.29 (5H, m), 7.60 (1H, s).

### EXAMPLE 3

**(2R,3S,4S,8R)-2-(1-(1-(3,5-Bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(methanesulfonyloxy)methyl-3-phenyltetrahydropyran**

The compound of Example 2 (2.63mg) was dissolved in dichloromethane (20ml) and triethylamine (1.23ml) was added. Methanesulfonyl chloride (0.68ml) was added dropwise and the mixture was stirred for 1 hour. The mixture was washed with water, brine and dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to afford the title compound as a colourless oil (3.18g).

<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 1.46 (3H, d, J 6.6Hz), 1.79 (1H, dddd, J 12.0, 12.0, 12.0, 5.1Hz), 1.98 (1H, d br), 2.77 (3H, s), 2.77 (1H, dd, J 12.0, 3.1Hz), 2.87-2.97 (1H, m), 3.78-3.85 (2H, m), 4.02-4.10 (2H, m), 4.47 (1H, d, J 3.1Hz), 4.89 (1H, q, J 6.6Hz), 7.20 (2H, s), 7.23-7.34 (5H, m), 7.60 (1H, s).

### EXAMPLE 4

**(2R,3R,4R,8R)-2-(1-(1-(3,5-Bis(trifluoromethyl)phenyl)ethyl)oxy)-4-hydroxymethyl-3-phenyltetrahydropyran**

The title compound was prepared from isomer 4 in Example 1 by a procedure analogous to that described in Example 2.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 360MHz): δ 1.07(1H, t J 5.5Hz), 1.37(3H, d J 6.6Hz), 1.63(1H, m), 1.81(1H, dm), 1.97(1H, m), 2.55(1H, dd J 11.6Hz and 8.4Hz), 3.26(1H, m), 3.40(1H, m), 3.57(1H, td J 12.0Hz and 2.4Hz), 4.18(1H, dm), 4.25(1H, d J 8.4Hz), 4.95(1H, q J 6.6Hz), 7.03(1H, m), 7.18(2H, s), 7.22-7.27(3H, m),  
5 7.66(1H, s).

#### EXAMPLE 5

**(2R,3R,4R,8R)-2-(1-(1-(3,5-Bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(methanesulfonyloxy)methyl-3-phenyltetrahydropyran**

10 The title compound was prepared from the compound of Example 4 by a procedure analogous to that described in Example 3.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 360MHz): δ 1.37(3H, d J 6.6Hz), 1.73(1H, qd J 11.8Hz and 4.6Hz), 1.83(1H, dm, J 11.5Hz), 2.2(1H, m), 2.58(1H, dd J 11.7Hz and 8.3Hz), 2.83(3H, s), 3.56(1H, td J 12Hz and 2.5Hz), 3.80(1H, dd J 9.8Hz and 6.8Hz),  
15 3.94(1H, dd J 9.9Hz and 3.4Hz), 4.17(1H, dm J 11.9Hz), 4.24(1H, d J 8.3Hz), 4.95(1H, q J 6.59Hz), 7.04(2H, m), 7.17(2H, s), 7.27(3H, m), 7.67(1H, s).

#### EXAMPLE 6

**(2R,3R,4R,8R,9(3'R))-2-(1-(1-(3,5-Bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-ethoxycarbonyl-3-methylpiperidin-1-yl)methyl-3-phenyltetrahydropyran**  
20 and

#### EXAMPLE 7

**(2R,3R,4R,8R,9(3'S))-2-(1-(1-(3,5-Bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-ethoxycarbonyl-3-methylpiperidin-1-yl)methyl-3-phenyltetrahydropyran**  
25

A mixture of the compound of Example 5 (0.2g) and ethyl 3-methylpiperidine-3-carboxylate (Description 4, 0.2g) were heated at 90°C for 16 hours. The cooled residue was purified by chromatography on silica gel eluting with ethyl acetate  
30 in isohexane (5% to 10%) to give two separated diastereomers.

**Example 6** (faster eluting) **(2R,3R,4R,8R,9(3'R))-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-ethoxycarbonyl-3-methylpiperidin-1-yl)methyl-3-phenyltetrahydropyran**

<sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.06 (3H, s, CH<sub>3</sub>), 1.23 (3H, t, J 7.2Hz), 1.35 (3H, d, J 6.6Hz, CH<sub>3</sub>), 1.4-1.6 (5H, m), 1.62-1.79 (1H, m), 1.88-1.97 (5H, m), 2.33-2.38 (2H, m), 2.57-2.69 (1H, m), 3.49 (1H, brt), 4.08-4.14 (3H, m), 4.15 (1H, d, J 8.3Hz), 4.93 (1H, q, J 6.5Hz), 6.99-7.02 (2H, m), 7.15 (2H, s), 7.19-7.22 (3H, m), 7.65 (1H, s).

MS (ES<sup>+</sup>) m/z 602 (M+H, 100%).

**Example 7** (slower eluting) (2R,3R,4R,8R,9(3'S))-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-ethoxycarbonyl-3-methylpiperidin-1-yl)methyl-3-phenyltetrahydropyran

<sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 1.04(3H, s), 1.27(4H, m), 1.32(3H, d J 6.6Hz), 1.41-1.47(2H, m), 1.61-1.68(2H, m), 1.82-2.07(6H, m), 2.35(2H, dd J 10.3Hz and 8.3Hz), 2.95(1H, d J 10.7Hz), 3.54(1H td J 10.7Hz and 2.1Hz), 3.99-4.20(4H, m), 4.96(1H, q J 6.6Hz), 7.02(2H, m), 7.17(2H, s), 7.22-7.26(3H, m), 7.66(1H, s). MS (ES<sup>+</sup>) m/z 602 (M+H, 100%).

#### EXAMPLE 8

**(2R,3R,4R,8R,9(3'R))-2-(1-(1-(3,5-Bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-carboxy-3-methylpiperidin-1-yl)methyl-3-phenyltetrahydropyran**

The product of Example 6 (0.13g) was heated in methanol (3ml) and 4M-NaOH (0.5ml, aqueous) at 60°C for 16 hours. The solution was cooled to room temperature and the methanol removed by evaporation. The solution was adjusted to pH 7.0 by addition of solid CO<sub>2</sub> and then extracted with ethyl acetate (three times). The combined organic phases were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated to dryness. The residue was purified by chromatography on silica gel (eluting with increasing concentrations of CH<sub>2</sub>Cl<sub>2</sub>/MeOH/conc. aqueous NH<sub>3</sub> (100:10:0.4) in CH<sub>2</sub>Cl<sub>2</sub> (0% - 100%) to give the title compound as the free base.

<sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.09(3H, s), 1.35(3H, d J 6.6Hz), 1.45-1.75(5H, m), 1.90(2H, v broad d J 13.1Hz), 2.0(1H, d J 11.7Hz), 2.1-2.25(3H, m), 2.38(1H, dd J 11.2Hz and 9.2Hz), 2.75(1H, d J 11.8Hz), 2.90(1H, d J 9.2Hz), 3.55(1H, td J 12.1Hz and 2.2Hz), 4.16(1H dd J 12.0Hz and 3.1Hz), 4.95(1H q J 6.5Hz), 7.00(2H, m), 7.16(2H, s), 7.25(3H, m), 7.66(1H, s).



To a solution of the free base (87mg) in  $\text{CH}_2\text{Cl}_2$  was added 1M-ethereal HCl (0.16ml). The solution was evaporated to dryness and the product as the **hydrochloride salt** crystallised from diethyl ether.

mp 166-167°C.

- 5  $^1\text{H}$  NMR (400MHz, MeOH)  $\delta$  1.19 (3H, s,  $\text{CH}_3$ ), 1.33 (3H, d, J 6.6Hz,  $\text{CH}_3$ ), 1.40 (1H, ddd, J 3.9, 3.9, 13.7Hz), 1.60-1.71 (2H, m), 1.76-1.81 (1H, m), 2.01-2.12 (2H, m), 2.45-2.51 (2H, m), 2.56 (1H, ddd, J 3.0, 3.0, 12.7Hz), 2.72 (1H, d, J 13.2Hz), 2.77 (1H, d, 12.4Hz), 3.01-3.07 (1H, m), 3.24-3.27 (1H, m), 3.50 (1H, d, J 12.4Hz), 3.69 (1H, ddd, J 1.9, 1.9, 12.0Hz), 4.17 (1H, dd, J 3.0, 12.0Hz), 4.42 (1H, d, J
- 10 7.8Hz), 5.04 (1H, q, J 6.5Hz), 7.15-7.17 (2H, m), 7.24-7.32 (3H, m), 7.33 (2H, s), 7.74 (1H, s).

MS (ES+) m/z 574 ( $\text{MH}^+$ , 100%).

#### EXAMPLE 9

- 15 **(2R,3R,4R,8R,9(3'S))-2-(1-(1-(3,5-Bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-carboxy-3-methylpiperidin-1-yl)methyl-3-phenyltetrahydropyran**

The product of Example 7 (0.087g) was deprotected and isolated by a procedure analogous to that described for Example 8.

- $^1\text{H}$  NMR (360MHz,  $\text{CDCl}_3$ )  $\delta$  1.08 (3H, s), 1.35 (3H, d J 5.9Hz), 1.54 (1H, ddd J 11.1Hz and 3.6Hz), 1.60 (2H, d J 11.7Hz), 1.88 (2H, m), 2.0-2.2 (4H, m), 2.32 (2H, m), 2.87(m), 3.56 (td J 11.0Hz and 1.6Hz), 4.12 (2H, m), 4.21(1H, d J 7.5Hz), J 4.94(1H, q J 5.9Hz), 7.01(2H, m), 7.16(2H s), 7.26(3H, m), 7.66(1H, s).
- 20

MS (ES+) m/z 574 ( $\text{MH}^+$ , 100%).

- 25 To a solution of the free base (74mg) in  $\text{CH}_2\text{Cl}_2$  was added 1M-ethereal HCl (0.16ml). The solution was evaporated to dryness and the product as the **hydrochloride salt** crystallised from ethyl acetate.
- mp 166°C.

**(2R,3R,4R,8R,9(3'R))-2-(1-(1-(3,5-Bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-carboxy-3-methylpiperidin-1-yl)methyl-3-(4-fluorophenyl)tetrahydropyran**

Prepared by methods analogous to those described in Example 8 from  
5 corresponding intermediates containing the 4-fluorophenyl group.

<sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.16-1.20 (3H, s), 1.34 (3H, d, J 6.6Hz), 1.37-1.48 (1H, m), 1.55-1.84 (3H, m), 2.08 (2H, t, J 14.0Hz), 2.40-2.63 (3H, m), 2.69 (1H, d, J 13.1Hz), 2.78 (1H, d, J 12.4Hz), 3.04 (1H, dd, J 13.4, 9.5Hz), 3.46-3.55 (1H, m), 3.68 (1H, td, J 12.0, 1.9Hz), 4.15 (1H, dd, J 11.9, 2.9Hz), 4.37 (1H, d, J 7.7Hz),  
10 5.04 (1H, q, J 6.5Hz), 7.01 (2H, t, J 8.7Hz), 7.16-7.20 (2H, m), 7.34 (2H, s), 7.76 (1H, s).

MS (ES+) m/z 592 (MH<sup>+</sup>, 100%).

#### EXAMPLE 11

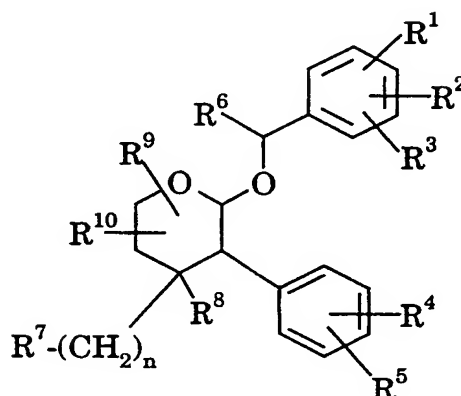
15 **(2R,3R,4R,8R,9(3'S))-2-(1-(1-(3,5-Bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-carboxy-3-methylpiperidin-1-yl)methyl-3-(4-fluorophenyl)tetrahydropyran**

Prepared by methods analogous to those described in Example 9 from  
corresponding intermediates containing the 4-fluorophenyl group.

20 MS (ES+) m/z 592 (MH<sup>+</sup>, 100%).

## CLAIMS:

1. A compound of the formula (I):



(I)

wherein

$R^1$  is hydrogen, halogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, fluoro $C_{1-6}$ alkyl, fluoro $C_{1-6}$ alkoxy,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-4}$ alkyl,  $NO_2$ , CN,  $SR^a$ ,  $SOR^a$ ,  $SO_2R^a$ ,  $CO_2R^a$ ,  $CONR^aR^b$ ,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl or  $C_{1-4}$ alkyl substituted by  $C_{1-4}$ alkoxy, wherein  $R^a$  and  $R^b$  each independently represent hydrogen or  $C_{1-4}$ alkyl;

$R^2$  is hydrogen, halogen,  $C_{1-6}$ alkyl, fluoro $C_{1-6}$ alkyl or  $C_{1-6}$ alkoxy substituted by  $C_{1-4}$ alkoxy;

$R^3$  is hydrogen, halogen or fluoro $C_{1-6}$ alkyl;

$R^4$  is hydrogen, halogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy, fluoro $C_{1-6}$ alkyl, fluoro $C_{1-6}$ alkoxy, hydroxy,  $NO_2$ , CN,  $SR^a$ ,  $SOR^a$ ,  $SO_2R^a$ ,  $CO_2R^a$ ,  $CONR^aR^b$ ,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl or  $C_{1-4}$ alkyl substituted by  $C_{1-4}$ alkoxy, wherein  $R^a$  and  $R^b$  are as previously defined;

$R^5$  is hydrogen, halogen,  $C_{1-6}$ alkyl, fluoro $C_{1-6}$ alkyl or  $C_{1-6}$ alkoxy substituted by  $C_{1-4}$ alkoxy;

$R^6$  represents hydrogen or a  $C_{1-4}$ alkyl group optionally substituted by a hydroxy group;

$R^7$  represents halogen, hydroxy,  $C_{2-4}$ alkenyl,  $N_3$ ,  $-NR^{11}R^{12}$ ,  $-NR^aCOR^b$ ,  $-OSO_2R^a$ ,  $-(CH_2)_pNR^a(CH_2)_qCOOR^b$ ,  $COR^a$ ,  $COOR^a$ , or a five membered or six

membered nitrogen-containing heteroaromatic ring optionally containing 1, 2 or 3 additional heteroatoms selected from N, O and S which heteroaromatic ring is optionally substituted at any substitutable position by a substituent selected from =O, =S, halogen, hydroxy, -SH, COR<sup>a</sup>, CO<sub>2</sub>R<sup>a</sup>, -ZNR<sup>11</sup>R<sup>12</sup>, C<sub>1-4</sub>alkyl,

5 hydroxyC<sub>1-4</sub>alkyl, fluoroC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, fluoroC<sub>1-4</sub>alkoxy or C<sub>1-4</sub>alkoxy substituted by a C<sub>1-4</sub>alkoxy or hydroxyl group;

R<sup>8</sup> represents hydrogen, C<sub>1-6</sub>alkyl, fluoroC<sub>1-6</sub>alkyl, hydroxy, C<sub>1-6</sub>alkoxy or hydroxyC<sub>1-6</sub>alkyl;

10 R<sup>9</sup> and R<sup>10</sup> each independently represent hydrogen, halogen, C<sub>1-6</sub>alkyl, CH<sub>2</sub>OR<sup>c</sup>, oxo, CO<sub>2</sub>R<sup>a</sup> or CONR<sup>a</sup>R<sup>b</sup> where R<sup>a</sup> and R<sup>b</sup> are as previously defined and R<sup>c</sup> represents hydrogen, C<sub>1-6</sub>alkyl or phenyl;

R<sup>11</sup> is hydrogen, C<sub>1-4</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkyl substituted by a C<sub>1-4</sub>alkoxy or hydroxyl group, or R<sup>11</sup> is a five membered or six membered nitrogen-containing heteroaromatic ring as previously defined;

15 R<sup>12</sup> is hydrogen or C<sub>1-4</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub>alkyl, or C<sub>2-4</sub>alkyl substituted by a C<sub>1-4</sub>alkoxy or hydroxyl group;

or R<sup>11</sup>, R<sup>12</sup> and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy, COR<sup>e</sup>, CO<sub>2</sub>R<sup>e</sup>, C<sub>1-4</sub>alkyl optionally substituted by a C<sub>1-4</sub>alkoxy or hydroxyl group, or C<sub>1-4</sub>alkoxy optionally substituted by a C<sub>1-4</sub>alkoxy or hydroxyl group, or a five membered or six membered nitrogen-containing heteroaromatic ring as previously defined, or said heteroaliphatic ring is substituted by a spiro-fused lactone ring, and said heteroaliphatic ring optionally containing a double bond, which heteroaliphatic ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or S(O)<sub>2</sub> or a second nitrogen atom which will be part of a NH or NR<sup>d</sup> moiety, where R<sup>d</sup> is C<sub>1-4</sub>alkyl optionally substituted by hydroxy or C<sub>1-4</sub>alkoxy, and where R<sup>e</sup> is hydrogen, C<sub>1-4</sub>alkyl or benzyl;

25 or R<sup>11</sup>, R<sup>12</sup> and the nitrogen atom to which they are attached form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

30 or R<sup>11</sup>, R<sup>12</sup> and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms to which is fused a benzene ring or a five membered or six membered nitrogen-containing heteroaromatic ring optionally containing 1, 2 or 3 additional heteroatoms selected from N, O and S;

Z represents a bond, C<sub>1-6</sub>alkylene or C<sub>3-6</sub>cycloalkylene;

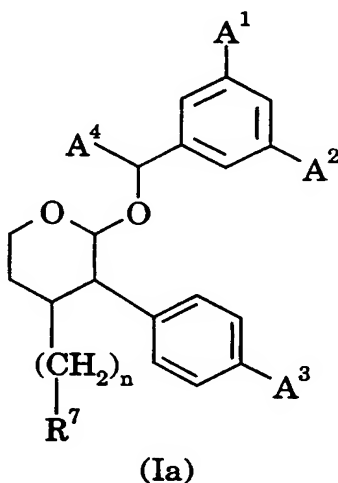
n is zero, 1 or 2;

p is 1 or 2; and

q is 1 or 2;

5 and pharmaceutically acceptable salts thereof.

2. A compound of the formula (Ia):



10

wherein

A<sup>1</sup> is fluorine or CF<sub>3</sub>;

A<sup>2</sup> is fluorine or CF<sub>3</sub>;

A<sup>3</sup> is fluorine or hydrogen;

15 A<sup>4</sup> is methyl or hydroxymethyl; and

R<sup>7</sup> and n are as defined in Claim 1;

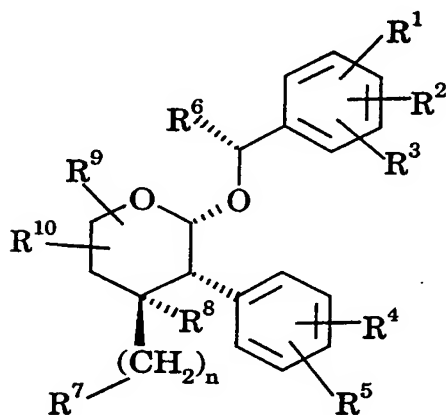
or a pharmaceutically acceptable salt thereof.

3. A compound as claimed in Claim 1 selected from:

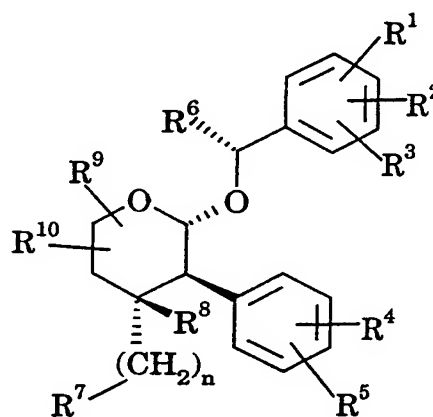
- 20 (2R,3S,4S,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(methanesulfonyloxy)methyl-3-phenyltetrahydropyran;
- (2R,3R,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-hydroxymethyl-3-phenyltetrahydropyran;
- (2R,3R,4R,8R)-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-
- 25 (methanesulfonyloxy)methyl-3-phenyltetrahydropyran;

- (2R,3R,4R,8R,9(3'R))-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-ethoxycarbonyl-3-methylpiperidin-1-yl)methyl-3-phenyltetrahydropyran;  
 (2R,3R,4R,8R,9(3'S))-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-ethoxycarbonyl-3-methylpiperidin-1-yl)methyl-3-phenyltetrahydropyran;  
 5 (2R,3R,4R,8R,9(3'R))-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-carboxy-3-methylpiperidin-1-yl)methyl-3-phenyltetrahydropyran;  
 (2R,3R,4R,8R,9(3'S))-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-carboxy-3-methylpiperidin-1-yl)methyl-3-phenyltetrahydropyran;  
 10 (2R,3R,4R,8R,9(3'R))-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-carboxy-3-methylpiperidin-1-yl)methyl-3-(4-fluorophenyl)tetrahydropyran; and  
 (2R,3R,4R,8R,9(3'S))-2-(1-(1-(3,5-bis(trifluoromethyl)phenyl)ethyl)oxy)-4-(3-carboxy-3-methylpiperidin-1-yl)methyl-3-(4-fluorophenyl)tetrahydropyran;  
 or a pharmaceutically acceptable salt thereof.

- 15 4. A compound as claimed in Claim 1 wherein the stereochemistry of the 2-, 3-, 4- and 8-positions is as shown in formulae (Ib) and (Ic):



(Ib)



(Ic)

20

5. A compound as claimed in any preceding claim for use in therapy.

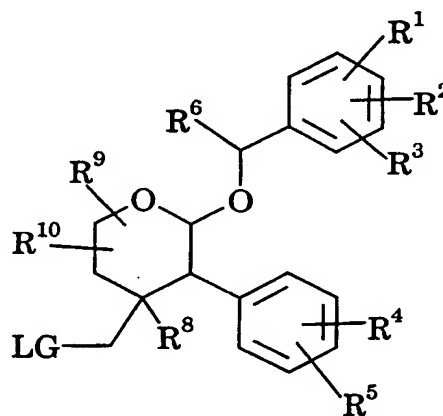
6. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 4, together with at least one pharmaceutically acceptable carrier or excipient.

5 7. A method for the treatment or prevention of pain or inflammation, migraine, emesis, postherpetic neuralgia, depression or anxiety, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound as claimed in any one of Claims 1 to 4.

10 8. The use of a compound as claimed in any one of Claims 1 to 4 for the manufacture of a medicament for the treatment or prevention of pain or inflammation, migraine, emesis, postherpetic neuralgia, depression or anxiety.

9. A process for the preparation of a compound as claimed in Claim 1  
15 which comprises:

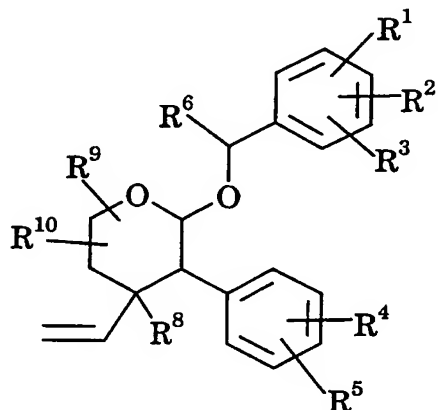
(A), where n is 1, reaction of a compound of formula (II)



(II)

20 wherein LG is a suitable leaving group; with an appropriate amine of the formula HNR<sup>11</sup>R<sup>12</sup>, or a heteroaromatic compound suitable for the addition of a five or six-membered nitrogen containing heteroaromatic ring as defined in relation to Claim 1, or an azide; or

(B), where  $R^7$  is hydroxy and  $n$  is 1 or 2, interconversion of a corresponding compound of formula (I) in which  $n$  is zero and  $R^7$  is vinyl, hereinafter referred to as formula (III)



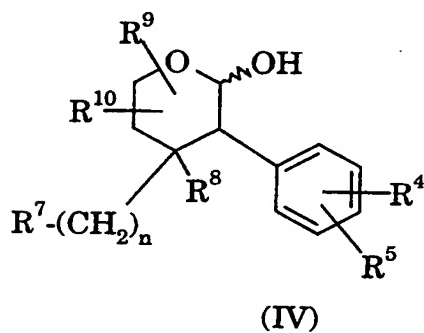
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(III)

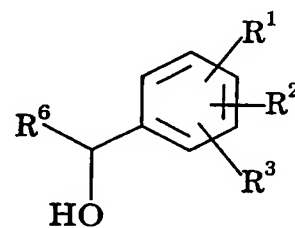
by reaction with ozone, followed by a reaction with a reducing agent, or by reaction with a reducing agent followed by hydrogen peroxide in the presence of a base; or

10

(C) reaction of a compound of formula (IV) with a compound of formula (V)



(IV)

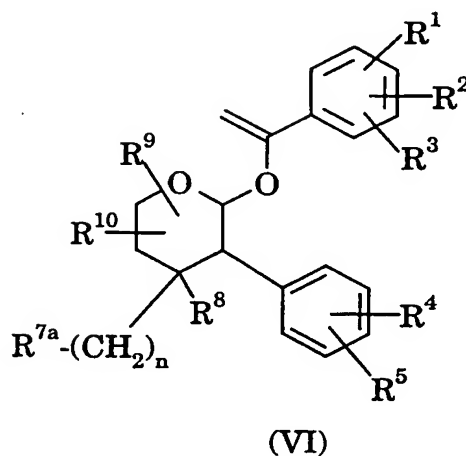


(V)

15 in the presence of a resin catalyst; or

(D), where  $R^6$  is either methyl or hydroxymethyl, reaction of a compound of formula (VI)





wherein  $R^{7a}$  is as defined for  $R^7$  in relation to Claim 1 or a precursor thereof;

5 under either:

- (a) (where  $R^6$  is methyl) catalytic hydrogenation conditions; or
- (b) (where  $R^6$  is hydroxymethyl) reducing conditions followed by

treatment with hydrogen peroxide and a base;

10 each process being followed, where necessary, by the removal of any protecting group where present;

and when the compound of formula (I) is obtained as a mixture of enantiomers or diastereoisomers, optionally resolving the mixture to obtain the desired enantiomer;

15 and/or, if desired, converting the resulting compound of formula (I) or a salt thereof, into a pharmaceutically acceptable salt thereof.

PCT Application No  
PCT/00/00977

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D309/10 C07D405/06 A61K31/351 A61P25/22

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EP0-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A. YAMASHITA: "SYNTHESIS OF CYCLOPENTANONES" TETRAHEDRON LETTERS., vol. 29, no. 28, 1988, pages 3403-6, XP002142389 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM., NL ISSN: 0040-4039 example 15; table SCH.3	1
A	EP 0 610 059 A (GORINSKI, C.) 10 August 1994 (1994-08-10) page 0; claims	1,5-8

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

13 July 2000

Date of mailing of the international search report

28/07/2000

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Francois, J

Information on patent family members		International Application No PCT/GB00/00977	
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 610059 A	10-08-1994	US 5786385 A	28-07-1998

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